No.:WSPC01 – 027

# Pharmacokinetics and tolerability of sublingual fentanyl in healthy Japanese and Caucasian volunteers: Phase I, open-label, single-dose study

Ulrike Lorch[1], Fiona Farrell[2], John Kilborn[2], Masami Tamaoka[3], Rob Derrick[4], Julian Howell[4]

[1]Richmond Pharmacology Ltd, St George's University of London, Cranmer Terrace, Tooting, London, SW17 0RE, UK
[2]Kyowa Hakko UK Ltd, Bath Road, Slough, Berkshire, SL1 4DX, UK
[3]Kyowa Hakko Kogyo Co. Ltd, 1-6-1 Ohtemachi, Chiyoda-ku, Tokyo 100-8185, Japan
[4]ProStrakan Group plc, Galabank Business Park, Galashiels, TD1 1QH, UK

## Background

- Breakthrough pain (BTP) is a transitory exacerbation of severe pain occurring on a background of otherwise controlled persistent pain.[1]
- Oral transmucosal fentanyl citrate, an opioid with rapid onset of action, is recommended as a supplement to the fixed-opioid schedule in the treatment for BTP.[2,3]
- Sublingual fentanyl (SLF) is a new rapidly disintegrating transmucosal delivery formulation of fast-acting fentanyl citrate developed for the management of BTP in opioid-tolerant cancer patients.
- Previously reported data show that SLF:
  - has favourable pharmacokinetic (PK) and tolerability profiles[4]
  - is quickly absorbed from the sublingual mucosa into the systemic circulation[5]
  - consists of an interactive mixture of carrier particles and fentanyl citrate with a bioadhesive component to minimise the potential for swallowing and absorption through the gastrointestinal tract[5]
  - allows for convenient and independent patient administration.[6]

## Objectives

- The objectives of this study were to:
  - determine the PK and tolerability profiles of single-dose SLF in healthy male Japanese and Caucasian subjects
  - assess whether differences in the rate and extent of fentanyl absorption and elimination exist between different ethnic groups.

## Methods

- This was a Phase I, UK-based, single-centre, open-label study consisting of four ascending single-dose treatment periods (Figure 1).

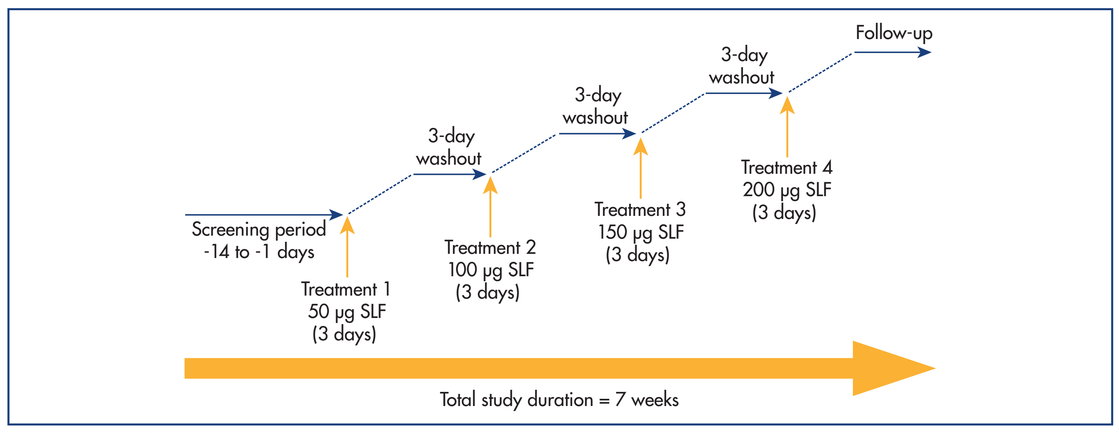


**Figure 1.** Study design

### *Study population*

- Twenty-one healthy male Japanese and Caucasian volunteers aged 20–45 years were recruited. Subjects had to have a body weight of 55–85 kg, with a body mass index of 18–25 kg/m$^2$, and be non-smokers or light smokers.
- Subjects with any relevant clinically significant, abnormal clinical history, any major illness within 3 months of study start or a history of opioid intolerance or severe allergic disease were excluded. Subjects using any medications within 5 days of study start or any concomitant medications, excluding anti-emetics and naloxone, were also excluded.

### *Treatment*

- Following a 2–14-day screening phase, subjects received a single ascending dose of SLF (50, 100, 150 and 200 µg) at each of the four treatment periods.
- Treatment periods were 3 days in duration, with each being separated by a ≥3-day washout period.
- At each treatment visit, blood and urine samples were collected at regular intervals for 24 hours after treatment administration.
- Subjects were monitored continuously throughout the study for signs of adverse events (AEs).

### *Assessments*

- The primary PK parameters included:
  - maximum plasma concentration of fentanyl ($C_{max}$)
  - time to $C_{max}$ ($t_{max}$)
  - time to first measurable plasma concentration of fentanyl ($t_{first}$)
  - area under the plasma concentration versus time curve from time 0 to the last quantifiable sampling point ($AUC_{0–t}$)
  - area under the plasma concentration versus time curve from time 0 extrapolated to infinity ($AUC_{0–\infty}$)
  - terminal half-life of the drug ($t_{1/2}$).

### *Statistical analysis*

- The study was designed to include 10 evaluable Japanese subjects and 10 evaluable Caucasian subjects.
- Individual PK parameters were determined using non-compartmental methods.
- All patients were to be included in the safety analysis.

## Results

### *Baseline demographics and characteristics*

- A total of 20 subjects completed all four treatment periods.
- One subject (Caucasian) was withdrawn following a positive drug test result prior to treatment period 2.
- No clinically relevant differences in demographic characteristics were noted between the ethnic groups (Table 1).

| Ethnic group | Number of subjects | Age Mean, years | Weight Mean, kg | Height Mean, m | BMI Mean, kg/m$^2$ |
|---|---|---|---|---|---|
| Caucasian | 11 | 25.7 ± 5.61 (20–38) | 69.17 ± 7.41 (56.6–79.9) | 1.77 ± 0.06 (1.69–1.87) | 22.09 ± 2.03 (19.40–25.15) |
| Japanese | 10 | 26.7 ± 3.02 (23–34) | 65.47 ± 7.04 (55.4–81.0) | 1.72 ± 0.07 (1.59–1.83) | 22.17 ± 1.65 (18.78–24.19) |
| Japanese & Caucasian | 21 | 26.2 ± 4.48 (20–38) | 67.41 ± 7.30 (55.4–81.0) | 1.75 ± 0.07 (1.59–1.87) | 22.13 ± 1.81 (18.78–25.15) |

**Table 1.** Baseline demographics (all 21 recruited subjects; ranges are shown in brackets). BMI: body mass index.

### *Mean plasma concentration–time curves*

- The mean plasma concentration–time curves (Figure 2) showed rapid absorption of fentanyl.

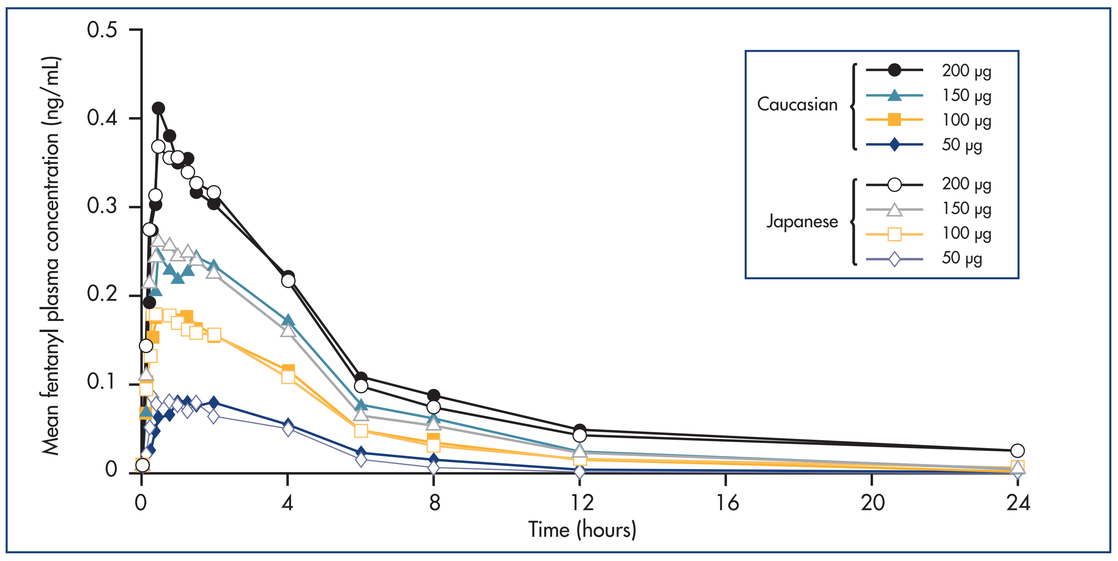


**Figure 2.** Mean fentanyl plasma concentration versus time in healthy male Japanese and Caucasian subjects

- No major differences were observed in plasma fentanyl levels between the ethnic groups.

### *Fentanyl pharmacokinetics*

- Overall mean PK parameters are given in Table 2.
- For all four doses, fentanyl was first quantifiable in plasma (median $t_{first}$) approximately 10–15 minutes after treatment, and median $t_{max}$ was 30–45 mins for all doses.
- $AUC_{0–t}$ and $C_{max}$ increased with ascending SLF dose.

| Pharmacokinetic variable | SLF dose 50 µg | 100 µg | 150 µg* | 200 µg |
|---|---|---|---|---|
| **Caucasian population** | | | | |
| $AUC_{0–t}$ (ng.h/mL) | 0.372±0.1375 | 0.915±0.3339 | 1.473±0.5846 | 2.319±0.9542 |
| $AUC_{0–\infty}$ (ng.h/mL) | 0.544±0.0663 | 1.033±0.2269 | 1.659±0.6110 | 2.803±1.3071 |
| $C_{max}$ (ng/mL) | 0.097±0.0309 | 0.219±0.0608 | 0.292±0.0976 | 0.452±0.1439 |
| $t_{max}$ (minutes)** | 60.0 | 30.0 | 45.0 | 37.5 |
| $t_{first}$ (minutes)** | 19.98 | 10.02 | 10.02 | 10.02 |
| $t_{1/2}$ (hours) | 3.457±1.3234 | 3.048±0.9663 | 4.711±2.4730 | 7.607±3.7779 |
| **Japanese population** | | | | |
| $AUC_{0–t}$ (ng.h/mL) | 0.321±0.1853 | 0.932±0.5576 | 1.425±0.8476 | 2.203±1.2461 |
| $AUC_{0–\infty}$ (ng.h/mL) | 0.672±0.2218 | 1.060±0.7439 | 1.768±1.1324 | 1.973±1.0147 |
| $C_{max}$ (ng/mL) | 0.110±0.0387 | 0.219±0.0650 | 0.301±0.0711 | 0.412±0.1484 |
| $t_{max}$ (minutes)** | 37.98 | 30.0 | 30.0 | 52.5 |
| $t_{first}$ (minutes)** | 12.48 | 10.02 | 7.5 | 10.02 |
| $t_{1/2}$ (hours) | 3.327±0.9244 | 4.133±3.6026 | 4.858±3.7805 | 5.792±3.3680 |
| **All subjects** | | | | |
| $AUC_{0–t}$ (ng.h/mL) | 0.347±0.1610 | 0.923±0.4474 | 1.449±0.7090 | 2.261±1.0818 |
| $AUC_{0–\infty}$ (ng.h/mL) | 0.592±0.1446 | 1.047±0.5472 | 1.720±0.9145 | 2.416±1.2161 |
| $C_{max}$ (ng/mL) | 0.104±0.0347 | 0.219±0.0613 | 0.297±0.0832 | 0.432±0.1437 |
| $t_{max}$ (minutes)** | 45.0 | 30.0 | 30.0 | 45.0 |
| $t_{first}$ (minutes)** | 15.0 | 10.02 | 10.02 | 10.02 |
| $t_{1/2}$ (hours) | 3.397±1.1119 | 3.623±2.6851 | 4.794±3.1740 | 6.760±3.5883 |

*One 50 µg tablet and one 100 µg tablet; **Median data

**Table 2.** Overview of the sublingual fentanyl pharmacokinetic data (mean±SD) for healthy male Japanese and Caucasian subjects

- While some degree of non-uniformity was observed across the four doses in $AUC_{0–\infty}$, $t_{max}$ and $t_{first}$, overall there was no trend to indicate statistically significant ethnic differences in the rate and extent of SLF absorption (p=0.6274, p=0.7162 and p=0.8943 for $AUC_{0–t}$, $AUC_{0–\infty}$ and $C_{max}$, respectively).

### *Tolerability profile of SLF*

- Thirty-nine AEs were reported by 13 subjects; all were mild to moderate in severity, and the majority were considered possibly or probably treatment-related.
- The most common AE was somnolence.
- The incidence of AEs increased in proportion to ascending SLF dose; however, no marked differences were observed between the ethnic groups (19 AEs reported by five Caucasian subjects and 20 reported by eight Japanese subjects).

## Conclusions

- Fentanyl plasma concentrations increased as a function of ascending dose.
- Plasma concentration data indicate that fentanyl was rapidly absorbed ($t_{first}$ and $t_{max}$), irrespective of ethnicity or dose.
- SLF had a good tolerability profile within these volunteers, with no differences attributable to ethnicity.
- The lack of ethnic differences in kinetics is encouraging and suggests that no specific modifications in dosing between Caucasian and Japanese subjects are needed.

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IM–M017/0002

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